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Fatal Differentiated Thyroid Cancer

TETSURO KOBAYASHI, MD, HIDEKI ASAKAWA, MD, YASUHIRO TAMAKI, MD, KOJI UMESHITA, MD, AND MORITO MONDEN, MD
From the Departments of Surgery II (T.K., Y.T., K.U., M.M.) and Internal Medicine II (H.A.), Osaka University Medical School, Osaka, Japan

Thirty-five patients who died of differentiated thyroid cancer were analyzed for factors affecting survival. The neck was the most common initial site of recurrence (62.0%). The lung was the most common metastatic site (56.7%). Major sites associated with death were locoregional recurrence (neck and mediastinum: 48.6%) and bone metastases (22.9%). By univariate analysis, local tumor extension, type of initial surgery, and residual tumor and/or existence of distant metastases at the initial operation were significant factors affecting survival. Stepwise multivariate analysis revealed that invasion of the esophagus and/or carotid artery shortened survival and that multiple surgeries extended survival. Our results suggest that to improve survival in patients with differentiated thyroid cancer, better locoregional control, including multiple surgical resection, is necessary.

KEY WORDS: survival time, recurrence, metastasis, univariate analysis, multivariate analysis

INTRODUCTION

Differentiated thyroid cancer is generally not fatal [1–6]. Because of slow tumor growth, most physicians do not consider differentiated thyroid cancer a life-threatening disease, even if recurrence or distant metastases appear. However, when the surgical approach is limited by adhesions from repeated operations for recurrent neck tumors, or when distant metastatic lesions do not take up radioiodine, treatment options become limited, and the patient may die from the disease. AGES and AMES scores are well-known prognostic factors for differentiated thyroid cancer [7,8]. We investigated factors affecting survival in patients with differentiated thyroid cancer, focusing on fatalities, and compared our results to other generally recognized prognostic factors.

MATERIALS AND METHODS

From 1968 to 1990, 650 patients with thyroid cancer underwent operations in the Department of Surgery II, Osaka University Medical School, Thirty-five of these patients died (Table I). Patients with lymphoma, medullary, or anaplastic cancer were excluded from this series. There were 10 men and 25 women, ranging in age from 21 to 81 years at the initial operation (mean 58.1 years, median 61.5 years). Total or subtotal thyroidectomy was performed initially in 25 patients (25/35, 71.4%), while a lobectomy or lesser surgery was performed in 10 (10/35, 28.6%). Histologic examination of the resected specimens from the initial surgeries showed papillary carcinoma in 28 patients (28/35, 80%) and follicular carcinoma in 7 patients (7/35, 20%). Lymph node involvement was divided into three groups: right cervical, left cervical, or paratracheal involvement. The number of operations each patient underwent ranged from 1 to 10 (median 2). Three patients underwent vertebral replacement and fixation, and 2 patients underwent reconstruction of the esophagus. Internal radiotherapy was given to 9 patients (54–355 mCi). Seven patients had tumors that did not take up radioiodine. The other 19 patients were not examined for iodine uptake. External beam radiotherapy was given to 15 patients (15/35, 42.9%). Ten patients had residual tumor or distant metastases at their first operation. Tumor extension in the neck was evaluated during the initial surgery. Six patterns of invasion were noted: muscle, trachea and/or larynx, recurrent nerve, esophagus, jugular

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Address reprint requests to Dr. Tetsuro Kobayashi, Department of Surgery II, Osaka University Medical School, 2-2 Yamadaoka, Suita, Osaka 565, Japan.

TABLE I. Clinical and Demographic Data on 35 Patients Who Died of Differentiated Thyroid Cancer

Patient	Age/ sex[a]	Survival (yr)	Tumor		Surgery[c]	Histology[d]	Lymph node metastasis[e]	Recurrence[f]		No. of operations	Radio iodine (mCi)	Radiation (cGy)	Distant metastasis[g]	Cause of death[h]
			Size (cm)	Extension[b]				First site	Interval (yr)					
1	74/F	1	7.5	M,T,R,E,J	t-Tx	P	R,L,C	Brain	0	1	—	—	Brain (0), skin (0)	Brain
2	70/F	1	5	R	t-Tx	F	R*,C	Med	1	1	—	4,000	—	Med
3	69/F	1	>10	M,T,R,E,J,C	Lesser	P	R,L,C	Residual	0	1	—	—	—	Med
4	46/F	1	9	M,J,C	Lesser	P	L,C	Residual	0	1	—	—	—	Bone
5	73/F	2	8	T	t-Tx	P	R,L,C	Neck	1	1	—	—	Lung (2)	Med
6	67/F	2	8	M,T	t-Tx	P	R,L,C	Brain	2	1	—	—	Brain (2)	Brain
7	52/F	3	5.5	—	t-Tx	P	R,L*,C	Lung	0	2	355	7,640	Lung (0)	Cachexia
8	65/F	3	5	T,R,E	t-Tx	P	R,L,C	Lung	0	2	—	—	Lung (0)	Neck
9	34/M	4	2	M,J	t-Tx	P	R*,L	Neck	4	2	120	—	Lung (4)	Lung
10	58/M	4	3	J	t-Tx	P	L,C	Neck	3	2	—	3,000	Lung (4)	Med*
11	61/F	4	10	M,T,E	t-Tx	F	L,C	Bone	3	3	—	—	Bone (3)	Bone
12	73/F	4	5	M,T,R,E	t-Tx	P	L,C	Neck	1	3	—	—	Lung (3)	Lung
13	70/F	4	6	T	t-Tx	P	R,L,C	Neck	1	4	—	5,000	Bone (3)	Bone
14	67/F	4	8.5	T	t-Tx	F	R,L	Neck	1	2	200	4,000	Bone (4)	Neck
15	66/F	4	3	—	t-Tx	F	—	Bone	0	1	150	—	Bone (0)	Bone
16	56/M	4	5	T,R	t-Tx	P	R,L,C	Residual	0	1	—	—	Lung (0)	Med
17	81/F	5	4.5	R,C	Lesser	P	L,C	Residual	0	1	—	—	—	Neck
18	66/M	5	10	T,R,E,J	t-Tx	P	R,L,C	Residual	0	1	—	2,200	Lung (1)	Neck
19	43/F	5	2	M,R	t-Tx	P	R,L,C	Bone	4	1	—	2,500	Bone (4)	Bone
20	64/F	5	7	T	t-Tx	P	R,L,C	Neck	1	2	—	7,090	—	Med
21	76/F	6	4	R,J	t-Tx	P	R*	Neck	2	1	—	6,950	Lung (6), liver (6)	Cachexia
22	67/M	6	3	—	Lesser	P	—	Neck	2	4	—	—	—	Neck
23	62/F	7	2	M	t-Tx	P	L*,C	Brain	3	3	—	Unknown	Brain (3)	Brain
24	51/M	8	2	—	Lesser	P	—	Neck	4	4	—	5,320	—	Neck
25	61/F	8	1	J	t-Tx	P	R,L,C	Neck	3	2	300	5,200	Lung (7)	Neck
26	37/M	11	5.5	M,J	t-Tx	F	R,L,C	Neck	6	6	100	4,600	Bone (8), lung (11)	Cachexia
27	69/F	12	7	T,R,J	t-Tx	P	L*	Residual	0	2	—	—	—	Med
28	55/M	12	3	—	Lesser	F	—	Neck	6	4	200	—	—	Neck
29	32/M	12	2	—	Lesser	P	R,C	Neck	1	10	—	14,000	Lung (10)	Neck
30	21/F	13	6	—	Lesser	F	—	Neck	12	5	100	—	Lung (12), bone (12)	Bone
31	48/F	14	3	M,T,R	Lesser	P	R,C	Neck	10	4	—	—	—	Neck
32	53/F	15	2	—	Lesser	P	R,C	Neck	4	3	—	—	Bone (4), lung (6)	Bone
33	56/F	15	5	M,J	t-Tx	P	R,C	Lung	2	2	—	—	Lung (2)	Lung
34	66/M	15	4	M,T	t-Tx	P	R,L,C	Lung	6	1	—	—	Lung (6)	Lung
35	25/F	34	3	T,R	t-Tx	P	R,C	Neck	12	7	54	Unknown	Lung (26)	Bone

[a] F, female; M, male.

[b] M, muscle; T, trachea and/or larynx; R, recurrent nerve; E, esophagus; J, jugular vein; C, carotid artery.

[c] t-Tx, total or subtotal thyroidectomy; lesser, lobectomy, segmentectomy, or enucleation.

[d] P, papillary carcinoma; F, follicular carcinoma.

[e] R, right cervical neck; L, left cervical neck; C, pre- and paratracheal regions; *, lymph node larger than 5 cm.

[f] Med, mediastinum; Interval, time between the first surgery and the first recurrence.

[g] Parentheses, the period (years) between the appearance of distant metastasis and initial resection.

[h] Med*, death due to anaplastic cancer.

vein, and carotid artery. Most patients did not receive chemotherapy. Patient 10 died of an anaplastic cancer.

Statistical Analysis

Survival curves were constructed using the Kaplan–Meier method and analyzed using the log-rank test. The proportional hazard model of Cox was employed for risk factor analysis, and the relative importance of variables was expressed as the risk ratio and *P*-values. A step-up multiple regression analysis was performed with a linear model of variables that concerned the patients and their disease.

RESULTS

The neck was the most common site of first recurrence among the patients (18/25) who did not have residual tumor and/or distant metastasis at their initial resection (Table II). The interval to the neck recurrence ranged from 1 to 12 years (median 3 years). Distant metastases were seen in the lungs, bone, and brain, in that order of frequency. Seventeen patients died of causes related to tumor recurrence in the neck or mediastinum, indicating failure to control locoregional disease. Bony metastases caused death when metastases in the vertebrae caused spinal cord paralysis. Local tumor extension, the type of initial surgery, and residual tumor and/or the existence of distant metastases at initial resection were found to be significant factors affecting survival, by univariate analysis (Table III). Patients with cancer invading the esophagus and/or carotid artery had shorter survivals (Fig. 1). Residual tumor and/or the existence of distant metastases at the time of initial resection shortened survival strikingly (Fig. 2). Among the fatal cases, gender and radiotherapy did not affect survival. The appearance of distant metastasis following surgery also did not affect survival. Finally, local tumor extension and the existence of distant metastases at initial resection affected survival. The stepwise method of analysis clarified that the number of operations, and invasion of the esophagus and/or carotid artery significantly affected survival (Table IV).

TABLE II. Differentiated Thyroid Cancer: Tumor Recurrence and Death

Site	N
First recurrence	
Neck	18
Lung	4
Brain	3
Bone	3
Mediastinum	1
Distant metastases[a]	
Lung	17
Bone	8
Brain	3
Liver	1
Skin	1
Cause of death	
Neck	10
Bone	8
Mediastinum	7
Lung	4
Brain	3
Cachexia	3

[a]Some patients had multiple sites.

DISCUSSION

Analysis of the relationship of local recurrence, distant metastases, and the cause of death is essential to understanding the natural history of differentiated thyroid cancer. In our patients, the major site of first recurrence was the neck, and the major cause of death was locoregional disease, that is, disease involving the neck and mediastinum, although distant metastases, such as lung and bone metastases, also appeared in many patients. Smith et al. [9] reported that local recurrence is seen in almost all fatal cases of differentiated thyroid cancer. This finding indicates that local control is difficult to achieve in recurrent thyroid cancer. Noguchi et al. [10] have also reported that the causes of death in patients with thyroid cancer were distant metastasis for the excellent group, defined as having a disease-specific survival rate of about 99%, and local recurrence for the intermediate (survival rate, 95%) and poor groups (survival rate, 70%). In our study, the mean survival time was 6.2 years for patients dying of locoregional recurrence, compared with 8.2 years for those dying of distant metastases (Table I).

The median survival time was 5 years in our study. The 16 patients who survived less than 5 years underwent their initial resection at a mean age of 62.6 years and had a mean survival time of 2.9 years. By contrast, the 19 patients with a survival time of 5 or more years underwent their initial resection at a mean age of 54.4 years and had a mean survival time of 10.9 years. The mean age of death was 65.5 years in the first group and 65.3 years in the latter. The mean age of death did not differ significantly between these two groups. These results suggest that the interval from tumorgenesis to death is less variable in patients with differentiated thyroid cancer and that survival is inversely related to age at the time of the initial treatment.

Individual institutions do not have enough numbers of cases of differentiated thyroid cancer to study the disease, because of the low morbidity and long treatment periods. Therefore, prospective controlled trials for differentiated thyroid cancer are impractical [11,12]. Our study shows that the number of operations, and the extent of the tumor (invasion of the esophagus and/or carotid artery) affect survival in a multivariate analysis. In fact, in our study, four of eight patients with thyroid cancer invading the esophagus and/or carotid artery did not undergo a complete resection, and five of six patients with residual

TABLE III. Factors Affecting Survival in a Univariate Analysis of 35 Cases of Fatal Thyroid Cancer

Factor	No. of patients	Mean survival (yr)	50% survival (yr)	*P* log-rank test
Sex				0.5572
Male	10	8.10	7.00	
Female	25	6.92	4.00	
Tumor size				0.0581
≤3 cm	13	10.23	8.00	
>3 cm	22	5.50	4.00	
Site of primary lesion				0.4467
Right or left lobe	26	7.81	5.00	
Both	9	5.67	5.00	
Local tumor extension				0.0052
No	8	9.13	10.00	
Yes—esophagus (E) or carotid artery (A), not involved	19	8.26	5.00	
Yes—E or A, involved	8	3.00	3.50	
First surgery[a]				0.0069
Total or subtotal thyroidectomy	21	5.33	4.00	
Lesser surgery	8	14.25	12.50	
Residual tumor or distant metastasis at 1st surgery				0.0067
No	25	8.60	6.00	
Yes	10	3.90	3.50	
Lymph node metastasis				0.6668
No	5	8.60	8.00	
Yes	30	7.03	4.50	
Histology				0.7236
Papillary	28	7.32	5.00	
Follicular	7	7.00	4.00	
Distant metastasis				0.5895
No	9	6.33	5.00	
Yes	26	7.58	4.50	
^{131}I-uptake				0.7507
No	7	7.43	6.00	
Yes	9	10.33	8.00	
External radiation				0.9532
No	20	6.85	4.00	
Yes	15	7.80	5.00	
Cause of death				0.2919
Local	17	6.23	5.00	
Distant metastasis	18	8.22	4.50	

[a]Patients with residual tumor at initial resection are excluded.

TABLE IV. Factors Affecting Survival in a Multivariate Analysis of 35 Cases of Fatal Thyroid Cancer (Stepwise Method)

Factor	Risk ratio	*P*
No. of operations[a]	0.807	0.0444
Tumor extension[b]	3.275	0.0124

[a]Risk ratio for one more time increase of operation.
[b]Risk ratio between no invasion and invasion (E/C) group (E/C); (esophagus/carotid artery).

tumor had no other surgery. These factors suggest that a complete resection of the tumor at the initial surgery may be the most important factor affecting survival. Moreover, it appears to be better to resect recurrent tumors, if possible, because this improves survival. Although Hannequin et al. [13] have discussed the pitfalls of applying the

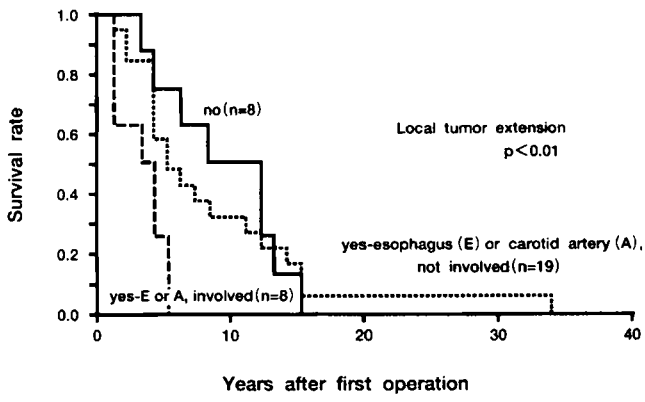

Fig. 1. Survival rate of 35 patients with fatal thyroid cancer, related to local tumor extension.

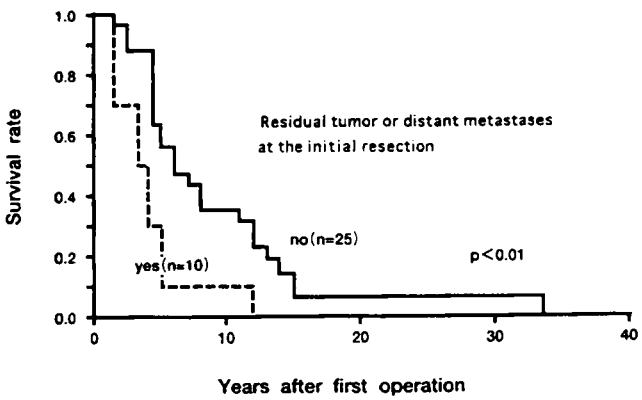

Fig. 2. Survival rate of 35 patients with fatal thyroid cancer, related to residual tumor or distant metastases at initial resection.

results of published studies to another population in a multifactorial analysis of survival in thyroid cancer, we compared our results with the well-known AGES and AMES scoring systems. We applied age, size, extent, and metastasis factors to our data. Considering age, most of the deaths (28/35, 80%) were in older patients (men, >40 years; women, >50 years). Patients with larger tumors appeared to have shorter survival times, although the statistical analysis was not significant ($P < 0.0581$). In fact, all the patients who died within 3 years had large tumors (>5 cm). Thirty patients had lymph node involvement in the neck at the time of their initial resection, and the 10 of those with invasion of the carotid artery and/or esophagus had a worse prognosis. Moreover, 10 patients with residual tumor and/or distant metastases at initial resection also had a worse prognosis. These facts are compatible with the AMES system [8].

Although radioiodine treatment is thought to be the most effective therapy for distant metastases of differentiated thyroid cancer [14], our data indicate that this therapy failed to affect survival. Considering the causes of death, approximately one-half of the patients (17/35) died of failed locoregional control, although 8 also had distant metastases. On the other hand, only 4 patients died of pulmonary metastases. Therefore, radioiodine therapy did not appear to affect survival.

CONCLUSION

We analyzed 35 deaths from well-differentiated thyroid cancer. Most of these patients had high risk factors according to the AMES system. One-half of the patients died of locoregional recurrences. To improve survival in differentiated thyroid cancer, better locoregional control is necessary.

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